



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/KR99/00530</p> <p>(22) International Filing Date: 8 September 1999 (08.09.99)</p> <p>(30) Priority Data: 1998/37181 9 September 1998 (09.09.98) KR</p> <p>(71) Applicant (for all designated States except US): HANMI PHARM. CO., LTD. [KR/KR]; #893-5, Hajeori, Paltan-myeon, Hwaseonggun, Kyungki-do 445-910 (KR).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): LEE, Tae, Suk [KR/KR]; Hanyang Apt., 603-709, Yangjimaoul, #29, Sunae-dong, Bundang-gu, Seongnam-shi, Kyungki-do 463-020 (KR). LEE, Ju, Cheol [KR/KR]; #633-7, Gui-1-dong, Kwangjin-gu, Seoul 143-201 (KR). LEE, Kyoung, Ik [KR/KR]; #542-1, Ganseok-1-dong, Namdong-gu, Incheon 405-231 (KR). LEE, Gwan, Sun [KR/KR]; Geuk-dong Apt., 2-806, Garak-dong, Songpa-gu, Seoul 138-160 (KR). KIM, Wan, Joo [KR/KR]; Olympicseonsuchon Apt., 311-1002, #89, Bangi-dong, Songpa-gu, Seoul 138-050 (KR).</p> <p>(74) Agents: JANG, Seong, Ku et al.; 17th floor, KEC Building, #275-7, Yangjae-dong, Seocho-ku, Seoul 137-130 (KR).</p>		<p>(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
(54) Title: METHOD OF PREPARING FORM II CRYSTALS OF CLARITHROMYCIN		
<p>(57) Abstract</p> <p>Form II crystals of clarithromycin can be easily prepared by treating clarithromycin of different crystal forms with water or with a mixture of water and a water-immiscible organic solvent and isolating treated crystals by filtration.</p>		

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## METHOD OF PREPARING FORM II CRYSTALS OF CLARITHROMYCIN

FIELD OF THE INVENTION

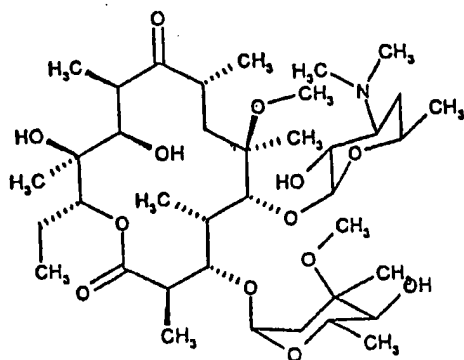
5       The present invention relates to a method of preparing Form II crystals of clarithromycin comprising treating clarithromycin with water to provide said crystals having no residual organic solvent.

10   BACKGROUND OF THE INVENTION

Clarithromycin, 6-O-methylerythromycin A, is a semisynthetic macrolide antibiotic of formula (I) which exhibits a wide range of antibacterial activity:

15

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(I)

It has been discovered that clarithromycin exists in two distinct crystalline forms, "Form I" and "Form II", as described in International Publication Nos. WO 98/04573 and WO 98/04574. The crystal forms can be identified by infrared spectroscopy, differential scanning calorimetry and powder x-ray diffraction spectrophotometry. Form I crystals of clarithromycin are prepared by recrystallization from ethanol, tetrahydrofuran, isopropyl acetate, isopropyl alcohol or a mixture thereof. However, the thermodynamically more stable Form II is used in the drug formulations currently on the market.

35       Form II crystals of clarithromycin have been prepared by crystallization from chloroform/isopropyl ether (1:2) (see Merck Index 12th ed., pp. 395), but this method has a

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problem in that the resulting Form II crystals contain residual organic solvents. Alternatively, Form II crystals may be obtained by heating Form I crystals under a vacuum at 80°C or higher for a prolonged time (see International Publication No. WO 98/04573), but this method has the problem of low productivity.

International Publication No. WO 98/04574 teaches a method of preparing clarithromycin crystal Form II using various organic solvent systems or aqueous solvents containing water-miscible organic solvents. However, this method is hampered by a relatively low yield (approximately 9 to 83%) and still has the problem of entrained organic solvents.

Accordingly, there has existed a need to develop a new simple method for preparing pure Form II crystals of clarithromycin in a high yield.

#### SUMMARY OF THE INVENTION

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Accordingly, it is a primary object of the present invention to provide pure Form II crystals of clarithromycin having no residual solvent in a high yield.

In accordance with the present invention, there is provided a method of preparing Form II crystals of clarithromycin comprising treating clarithromycin with water or with a mixture of water and a water-immiscible organic solvent.

#### BRIEF DESCRIPTION OF THE DRAWINGS

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The above and other objects and features of the present invention will become apparent from the following description, when taken in conjunction with the accompanying drawing wherein:

Fig. 1 shows the powder X-ray diffraction spectrum of clarithromycin crystal Form II.

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DETAILED DESCRIPTION OF THE INVENTION

The method of preparing Form II crystals of clarithromycin in accordance with the present invention  
5 comprises the step of treating clarithromycin with water or with a mixture of water and a water-immiscible organic solvent and isolating treated crystals.

The term "clarithromycin" as used herein refers to refined crystal Form I or mixtures of refined crystal Form  
10 I and Form II, or crude reaction product formed during the process of the preparation thereof. Representative methods of preparing clarithromycin are described in U.S. Patent Nos. 4,331,803, 4,670,549, 4,672,109 and 4,990,602, and European Patent No. 260 938.

15 The treating step in accordance with the present invention may be performed at an ambient temperature with stirring for a period sufficient to convert Form I crystals to Form II crystals of clarithromycin, e.g., about 1 to 4 hours.

20 Water which may be distilled or deionized water is used in the inventive process in an amount ranging from 3 to 10 times that of clarithromycin used.

The water-immiscible organic solvents optionally used in the present invention are those which do not dissolve  
25 clarithromycin to any significant extent, and examples thereof include C<sub>5-7</sub> hydrocarbons, diethyl ether, ethyl acetate, methyl acetate and the like. The optional water-immiscible organic solvent functions to dissolve impurities that may be present in a clarithromycin feed, thereby  
30 further increasing the purity of the product. The organic solvent may be employed in an amount ranging from 0.5 to 2 times that of clarithromycin used.

After the clarithromycin crystals are sufficiently treated, the resultant crystals are filtered and dried in a  
35 conventional manner to give pure clarithromycin crystal Form II in a high yield of at least 95%.

The method of the present invention is very simple and

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provides pure Form II crystals of clarithromycin having no residual organic solvent in a high yield of greater than 95% at a low process cost.

The following Examples are intended to further  
5 illustrate the present invention without limiting its scope.

Example 1 : Recovering of Form II crystals of clarithromycin from Water

100g of clarithromycin (purity: 95.5%) was added to  
10 500ml of water and the resulting mixture was stirred vigorously at room temperature for 2 hours. The crystals were filtered and dried overnight in a vacuum oven of 60°C to give 97g of clarithromycin crystal Form II (purity: 97.4%, yield: 97%).

15

Example 2 : Recovering of Form II crystals of clarithromycin from Water and Hexane

100g of clarithromycin (purity: 95.5%) was added to  
500ml of water and the resulting mixture was stirred  
20 vigorously at room temperature for 2 hours. 100ml of hexane was added thereto, and the mixture was further stirred at room temperature for 1 hour. The resulting crystals were filtered and dried overnight in a vacuum oven of 60°C to give 95g of clarithromycin crystal Form II (purity: 97.7%,  
25 yield: 95%).

Example 3 : Recovering of Form II crystals of clarithromycin from Water and Ethyl acetate

The procedure of Example 2 was repeated except that  
30 ethyl acetate was used instead of hexane, to give 95g of clarithromycin crystal Form II (purity: 98.0%, yield: 95%).

Example 4 : Recovering of Form II crystals of clarithromycin from Water and Methyl acetate

35 The procedure of Example 2 was repeated except that methyl acetate was used instead of hexane, to give 95g of clarithromycin crystal Form II (purity: 97.9%, yield: 95%).

- 5 -

Example 5 : Recovering of Form II crystals of clarithromycin from Water and Diethyl Ether

The procedure of Example 2 was repeated except that diethyl ether was used instead of hexane, to give 97g of  
5 clarithromycin crystal Form II (purity: 97.5%, yield: 97%).

The powder X-ray diffraction pattern of each clarithromycin obtained in Examples 1 to 5 was identical to that of clarithromycin crystal Form II shown in Figure 1.

10 While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended  
15 claims.

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What is claimed is:

1. A method of preparing Form II crystals of clarithromycin comprising treating a clarithromycin feed  
5 with water or with a mixture of water and a water-immiscible organic solvent and isolating treated crystals by filtration.
2. The method of claim 1, wherein the water-  
10 immiscible organic solvent is selected from the group consisting of a C<sub>5-7</sub> hydrocarbon, diethyl ether, ethyl acetate and methyl acetate.
3. The method of claim 1 or 2, wherein the water-  
15 immiscible organic solvent is hexane.
4. The method of claim 1, wherein water is used in an amount ranging from 3 to 10 times that of the clarithromycin feed.  
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5. The method of claim 1, wherein the water-immiscible organic solvent is used in an amount ranging from 0.5 to 2 times that of the clarithromycin feed.

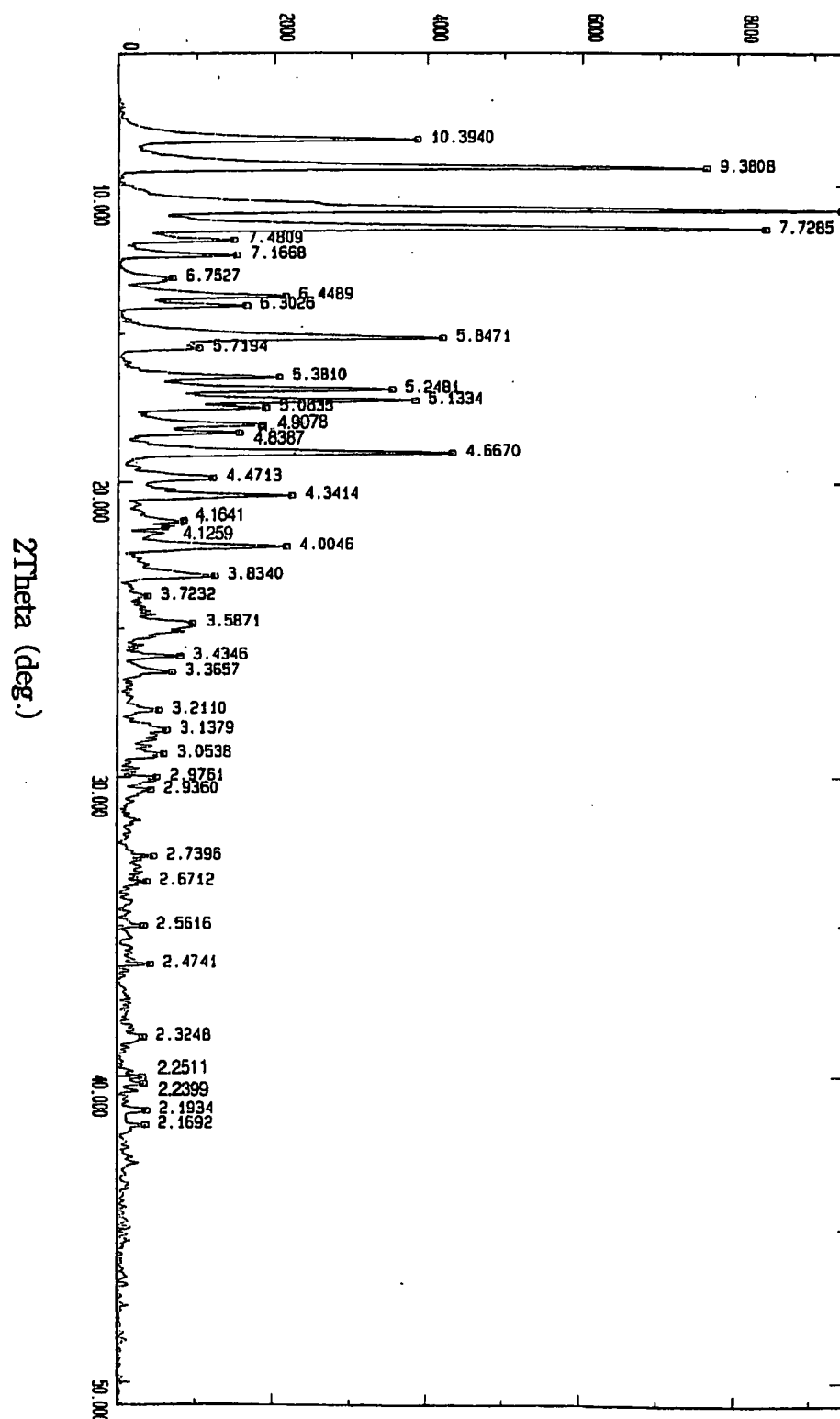
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Fig. 1

Intensity (cps)



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR 99/00530

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC <sup>7</sup> : C07H 17/08 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC <sup>7</sup> : C07H, A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WPI, CAS		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/04574 A1 (ABBOTT LABORATORIES) 05 February 1998 (05.02.98), claims. (Cited in the application).	1-5
A	WO 98/04573 A1 (ABBOTT LABORATORIES) 05 February 1998 (05.02.98), claims. (Cited in the applications).	1-5
A	WO 98/31699 A1 (ABBOTT LABORATORIES) 23 July 1998 (23.07.98), claims. <div style="text-align: center;">----</div>	1-5
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search 25 November 1999 (25.11.99)		Date of mailing of the international search report 21 January 2000 (21.01.00)
Name and mailing address of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200		Authorized officer Schnass Telephone No. 1/53424/217

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

PCT/KR 99/00530

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	A1	9804574	05-02-1998	AU	A1	37405/97	20-02-1998
				EP	A1	915899	19-05-1999
				US	A	5844105	01-12-1998
WO	A1	9804573	05-02-1998	AU	A1	37397/97	20-02-1998
				CA	AA	2258606	05-02-1998
				CN	A	1229411	22-09-1999
				CZ	A3	9900099	12-05-1999
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